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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,010	01/04/2002	Thomas M. Mills	M0351-267875	8818

7590 08/11/2004

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,010	MILLS ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-50* is/are pending in the application.

4a) Of the above claim(s) *21 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on April 27, 2004 wherein claims 1-11, 13-20 and 22-25 have been amended and claim 12 is cancelled.

Currently, claims 1-11 and 13-50 are pending in this application.

It is noted that claims 21 and 26-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, of record in the previous Office Action dated January 27, 2004.

Claims 1-11, 13-20 and 22-25 as amended now are examined on the merits herein.

Applicant's amendment amending claims 1-6 and 13-20, filed April 27, 2004 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of scope of enablement of record stated in the Office Action dated January 27, 2004 has been fully considered and is found persuasive to overcome the rejection as to claims 1-6 and 12-20 since the particular compound of formula (I) has been recited in the independent claim 1.

However, the rejection of claims 7-11 made under 35 U.S.C. 112 first paragraph for lack of scope of enablement of record stated in the Office Action dated January 27, 2004, is maintained as discussed further below.

Applicant's amendment and remarks filed April 27, 2004 with respect to the particular rejection of claims 1, 11, 12, and 25 made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitations, i.e., "an organ subject to sexual stimulation" in claim 1, "others" in claim 12, "potentiates" in claim 11, "certain drugs" and "such as" in claim 25 of record stated in the Office Action dated January 27, 2004 have been fully considered and found persuasive to remove the rejection as to claims 1, 11, 12, and 25, since claim 12 is cancelled; claim 25 has been amended; Applicant's remarks for "an organ subject to sexual stimulation", and citing the dictionary in regard to "potentiates" are found convincing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular compounds of formula (I) disclosed in the specification in co-administering the particular compounds such as sodium nitroprusside or NOR-1 employed in methods for particular treatments herein, does not reasonably provide enablement for co-administering the compound of formula (I) and any compounds represented by "a compound that reduces the amount of active Rho-kinase enzyme", or "a compound that

inhibits binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", for the claimed methods of treating male or female sexual dysfunction, for the same reasons of record in the previous Office Action January 27, 2004.

These recitations, "a compound that reduces the amount of active Rho-kinase enzyme", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" in these claims, are seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating male or female sexual dysfunction.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on any compounds represented by "a compound that reduces the amount of active Rho-kinase enzyme", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in the instant claims, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "a compound that reduces the amount of active Rho-kinase enzyme", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second

compound which potentiates the effects of nitric oxide" recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds of formula for each kind of functional compounds for the claimed method of treatment herein (see the specification 14, 15 and 30).

Thus, the instant specification fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be

unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treating male or female sexual dysfunction, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a male human), the *combination* of the compound of formula (I) and any compound represented by "a compound that reduces the amount of active Rho-kinase enzyme" of any compounds represented by "a compound that inhibits binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only those particular compounds of each functional groups are shown in the examples herein (see page 30 of specification for example). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the ingredients in the claimed method. See MPEP § 716.02(d).

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Response to Argument

Applicant's arguments filed April 27, 2004 with respect to the rejection of claims 7-9 made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement have been fully considered but are not deemed persuasive as further discussed below.

Applicants argue that "[W]ith respect to claims 7-9 describing the use of compounds that reduce the amount of active Rho-kinase activity, Applicants have described in the specification that guanine nucleoside dissociation inhibitors, such as known guanine nucleoside dissociation inhibitors RhOGDI-I, II, or III, bind cytosolic RIZOA to inhibit the release of GDP" and that with respect to claim 10, Applicants describe that it is known in the art that compounds such as sodium nitroprusside may be used to inhibit translocation of Rho A to the membrane" and that "with respect to claim 11, Applicants describe working examples of using compounds known to potentiate the effects of NO, such ms NOR-I and sodium nitroprusside, to add to the

effects of Y-27632". Applicants therefore assert that no undue experimentation would be required to practice the methods of amended claims.

Applicants' argument and assertion have been considered but not found convincing. As noted in MPEP 2111, during patent examination, claims are given their **broadest** reasonable interpretation. It is proper to use the specification to interpret what the applicant meant by a word or phrase recited in the claim, However, it is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994) for example.

In this case, the instant claims 7-11 are **not** limited to those known particular compounds or agents described in the specification. These claims read on any compounds represented by "a compound that reduces the amount of active Rho-kinase enzyme", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" employed in the claimed methods of treatment herein. These recitations broadly encompass those known and **unknown** and **future known** compounds having the recited functions as of the instant filing date. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds encompassed by claims herein must required to additional or future research to discover, establish, make and/or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Moreover, as discussed in the previous Office Action, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treating male or female sexual dysfunction, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a male human), the *combination* of the compound of formula (I) and any compound represented by "a compound that reduces the amount of active Rho-kinase enzyme" of any compounds represented by "a compound that inhibits binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", and/or while the patient also administering other medicines, in the absence of fully recognizing the identity of the members genus herein.

For the above stated reasons, said claims are properly rejected made under 35 U.S.C. 112, first paragraph, for lack of full scope of enablement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-20 and 22-25 as amended now are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention, of record in the previous Office Action January 27, 2004.

The recitation, "a functional derivative" in claim 1 renders claims 1-11, 13-20 and 22-25 indefinite. The recitation, "a functional derivative" is not clearly defined in the specification. Hence, one of ordinary skill in the art could not interpret the metes and bounds of the patent protection desired as to "a functional derivative" encompassed thereby.

The recitation "an individual" in claim 1 renders claims 1-11, 13-20 and 22-25 indefinite. The recitation "an individual" are not clearly defined in the specification. It is unclear as to the meaning of recitation "an individual" encompassed thereby.

Response to Argument

Applicant's arguments filed April 27, 2004 with respect to the rejection made under 35 U.S.C. 112, second paragraph, for indefinite recitations, i.e., "a functional derivative" and "an individual" have been fully considered but are not deemed persuasive as further discussed below.

Applicants assert that "an individual" is "a single human being" or "a person" as defined in the Oxford Dictionary and Thesaurus (American Edition, Oxford University Press, 1996). However, "an individual" is defined as "a particular being or thing as distinguished from a class, specie, or collection" which would encompass "a single human being" or "a person", or an animal, or "a single organism" (see the definition of "individual" provided by Merriam-Webster's College Dictionary 1998, page 593, PTO-892). Therefore, the claims are indefinite since one of ordinary skill in the art could not

ascertain and interpret the metes and bounds as to "an individual" as the patent protection desired in the instant invention.

Applicants assert that "a functional derivative is a compound derived from formula I that has the same biological function as the compounds of formula I", and that "common functional derivatives are the various salts and hydrates of formula I" and that "also included are compounds having modified functional groups where the modification does not reduce the functional activity". See Applicants' remarks at page 12. Applicant's argument and assertion are not found convincing to overcome this rejection.

First, the instant claims are not limited to the various salts and hydrates of formula I or those examples taught in US 4,997,834 as Applicants assert. Second, given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physical, chemical, and/or physiological properties and effects, one of ordinary skill in the art could not ascertain and interpret the metes and bounds as to "compounds having **modified** functional groups where the modification does not reduce the functional activity" as the patent protection desired in the instantly claimed invention. Thus, these claims are indefinite as to what functional derivatives of compounds herein would be encompassed thereby and employed in the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-20 and 22-25 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Muro et al. (US 4,997,834, of record) in view of the Merck Manual of Diagnosis and Therapy (17th ED) (page 1936-1837, of record) for the same reasons of record in the previous Office Action January 27, 2004.

Muro et al. discloses that the compounds of formula (I) which has covered and encompassed the elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract, col.2, col.8 lines 1-17 and 41-49) are useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities (see col.8 lines 19-27). Muro et al. discloses the effective dose of the compound with a pharmaceutically acceptable carrier to be administered to a hypertensive male (see col.8 lines 53 to col. 10 line 25).

Muro et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Muro et al. does not expressly disclose the method further comprising the active agent herein.

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can

result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compound of Muro et al. in methods of treating male or female sexual dysfunction.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ to employ the particular compound of Muro et al. in methods of treating male or female sexual dysfunction, because the particular compound of Muro et al is known to be useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities according to Muro et al. It is also known that hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction according to The Merck Manual of Diagnosis and Therapy (17th ED).

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound of Muro et al., would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also

treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Moreover, one of ordinary skill in the art would have reasonably expected that combining the active agent herein such as guanine nucleoside dissociation inhibitor (GDI) as a compound that inhibits GTP binding to RhoA enzyme recited in claim 9, sodium nitroprusside as the compound recited in claim 10, NOR-1, known useful for the same purpose, i.e., inhibiting RhoA, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments filed April 27, 2004 with respect to this rejection made under 35 U.S.C. 103(a) of record in the previous Office Action January 27, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicants argue that "Nowhere in Muro et al., however, is there an indication that compounds of formula I may be used to inhibit the activity of Rho-kinase". Applicants' argument is not found persuasive, since what Applicants argue here is deemed merely the mechanism of action of a treatment by administering the compound of formula (I) herein to a patient in need of such treatment. It is noted that the mechanism of action of a treatment, i.e., inhibiting the activity of Rho-kinase, does not

have a bearing on the patentability of the invention if the method steps are already known even though applicant has proposed or claimed the mechanism. Applicant's recitation of a new mechanism of action for the prior art method will not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

Applicants also argue that "Muro et al. and Merck suggest that compounds of formula I would be expected to have wide-ranging effects on systemic blood flow such as reducing hypertension and/or increasing coronary blood flow" and that "It is not clear that it would be beneficial to increase coronary and cerebral blood flow while attempting to treat sexual dysfunction", and that "the references provide no evidence that compounds of formula I are effective in treating sexual dysfunction".

Applicants' arguments are not found convincing. A chemical compound and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or substantially similar structure, the properties Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not inherently possess the same properties as instantly claimed. Applicant has not provided any evidence of record to show that the prior art compounds do not exhibit the same properties as instantly claimed.

Applicants further argue that Merck teaches away from using compounds of formula I to treat sexual dysfunction since Merck suggests that nitric oxide, not the instant compounds used in treating sexual dysfunction. Nonetheless, Merck has been

cited by the examiner primarily for its teaching that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can cause erectile dysfunction (a known sexual dysfunction).

Moreover, as discussed in the previous Office Action, the particular compound of Muro et al is known to be useful in methods of treating hypertension and abnormal of smooth muscles since these active compound possess coronary and cerebral blood flow-increasing activities according to Muro et al. It is also known that hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction according to the Merck Manual.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound of Muro et al., would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Most importantly, the patient population in Muro et al. is deemed to encompass, overlap, or coincide the patient in this claimed invention, in need of such a treatment of sexual dysfunction caused by hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Further, the record contains no clear and convincing evidence of nonobviousness or unexpected results for the claimed method herein over the prior art. In this regard, it is noted that the specification provides no side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art.

Claims 1-11, 13-20 and 22-25 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshii et al. (of record) in view of Uehata (EP 0 956 865, of record), further in view of the Merck Manual of Diagnosis and Therapy (17th ED) (page 1936-1837, of record). for the same reasons of record in the previous Office Action January 27, 2004.

Yoshii et al. discloses that the instant elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract) is the particular compound that attenuates RhoA kinase activity which can increase smooth muscle relaxation (see abstract). Yoshii et al. discloses that GTP is useful in combination with Y-27632 (see the abstract)

Yoshii et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Yoshii et al. does not expressly disclose the method further comprising the active agent herein.

Uehata (EP 0 956 865) discloses that the compounds of formula (III) which are structurally similar to Y-27632, as being RhoA kinase inhibitors, are useful in treating hypertension, vascular contraction, asthma in which smooth muscle contraction is involved and also treating fertilization and nidation of fertilized egg (see page 3 lines 13-20 and 30-34, page 8 lines 14-39).

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compound Y-27632 in methods of treating male or female sexual dysfunction.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ to employ the particular compound Y-27632 in methods of treating male or female sexual dysfunction, because Y-27632 is known to have RhoA kinase activity which can increase smooth muscle relaxation according to Yoshii et al. Moreover, the compounds of formula (III) of Uehata which are structurally similar to Y-27632, are known RhoA kinase inhibitors, are also known useful in treating hypertension, vascular contraction, asthma in which smooth muscle contraction is

involved and also treating fertilization and nidation of fertilized egg according to the Uehata patent. It is also known that hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction according to The Merck Manual of Diagnosis and Therapy (17th ED).

Further, Y-27632 would be expected to have similar activity or property as those compounds disclosed in Uehata patent based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound Y-27632 would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Moreover, one of ordinary skill in the art would have reasonably expected that combining the active agent herein such as guanine nucleoside dissociation inhibitor (GDI) as a compound that inhibits GTP binding to RhoA enzyme recited in claim 9, sodium nitroprusside as the compound recited in claim 10, NOR-1, known useful for the same purpose, i.e., inhibiting RhoA, would improve the therapeutic effects for treating

the same diseases, and/or would produce additive therapeutic effects in treating the same.

Response to Argument

Applicant's arguments filed April 27, 2004 with respect to this rejection made under 35 U.S.C. 103(a) of record in the previous Office Action January 27, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicants argue that "there is no description in Yoshii of Rho kinase activity in organs subject to sexual stimulation, such as the penis". Applicants further argue that "Nothing in Uehata, in combination with Yoshii teaches or suggests using Y-27632, or functional derivatives thereof, to specifically inhibit Rho-kinase in organs subject to sexual stimulation". Again, Applicants' arguments herein are deemed to be the mechanism of action of a treatment by administering the compound of formula (I) herein to a patient in need of such treatment. It is noted that the mechanism of action of a treatment, i.e., "in organs subject to sexual stimulation, such ms the penis", or inhibiting Rho-kinase in organs subject to sexual stimulation, does not have a bearing on the patentability of the invention if the method steps are already known even though applicant has proposed or claimed the mechanism. Applicant's recitation of a new mechanism of action for the prior art method will not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

A chemical compound and its properties are inseparable as discussed above. Therefore, if Yoshii et al. teaches the identical chemical structure compound, Y-27632,

or Uehata discloses the compounds of formula (III) which are structurally similar to Y-27632, as being RhoA kinase inhibitors, the properties Applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Applicants again argue that Merck teaches away from using compounds of formula I to treat sexual dysfunction. Nevertheless, Merck has been cited by the examiner primarily for its teaching that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can cause erectile dysfunction (a known sexual dysfunction).

Further, the patient population in Yoshii or Uehata is deemed to encompass, overlap, or coincide the patient herein in need of such a treatment of sexual dysfunction caused by hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
August 2, 2004

SHAOJIA ANNA JIANG
PATENT EXAMINER